II. REMARKS

Preliminary Remarks:

Amendment of the claims

Claims 20, 29, 55, 62, 68, and 75 are amended, new claims 80-92 are submitted, and claims 51-54, 58-61, 64-67, and 71-74 are canceled without prejudice. Claims 20, 29, 38-40, 55-57, 62, 63, 68-70, and 75-92 are currently pending.

Independent claim 20 is amended to incorporate the subject matter of claims 59 and 60, and independent claim 29 is amended to incorporate the subject matter of claims 72 and 73.

Claims 62 and 75 are amended to be directly dependent on amended claims 20 and 29, respectively, and claims 61 and 74 on which claims 62 and 75 previously depended are canceled. Direct fusion of the antibody C_H3 domain to the hinge region in the antibody heavy chain polypeptide as specified by claims 61 and 74 is a structural characteristic of the amino acid sequence of the heavy chain polypeptide sequence having SEQ ID NO:7 that is specified in claims 62 and 75.

New independent claim 80 corresponds to previously presented claim 20 which is amended to incorporate the subject matter of claim 62, and new independent claim 85 corresponds to previously presented claim 29 which is amended to incorporate the subject matter of claim 75.

New claims 81 to 84 depend on new claim 80, and correspond in subject matter to claims 55-57 and 63; and new claims 86 to 92 depend on new claim 85, and correspond in subject matter to claims 38-40 and 76-79.

Patentability Remarks:

Objections to the claims

The official action objected to claims 60, 62, 73, and 75 as being dependent upon a rejected base claim, but stated that the claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims (page 23, paragraph 29 of the official action). In response to this objection,

(a) independent claim 20 is amended to incorporate the subject matter of claims 59 and 60, and independent claim 29 is amended to incorporate the subject matter of claims 72 and 73;

(b) claims 62 and 75 are amended to be directly dependent on amended claims 20 and 29, and

(c) new independent claim 80 is submitted which corresponds to previous claim 20 that is amended to incorporate the subject matter of claim 62, and new independent claim 85 is

submitted which corresponds to previous claim 29 that is amended to incorporate the subject matter of claim 75.

The applicants submit that the foregoing amendment has re-written claims 60, 62, 73, and 75 in independent form including all of the limitations of the base claim and any intervening claims, and respectfully request that the objection to the claims be withdrawn.

35 U.S.C. §112, first paragraph

The official action rejected claims 54 and 67 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not provide evidence that hybridoma cells that produce the anti-TAG-72 antibodies specified in these claims are known and readily available to the public. The anti-TAG-72 antibodies specified in claims 54-67 are the subject of claim 44 of U.S. Patent No. 5,512,443. The applicants submit that the grant of U.S. Patent No. 5,512,443 by the United States Patent and Trademark Office with a claim that specifies hybridoma cells that produce the anti-TAG-72 antibodies in question is clear and sufficient evidence that the specified hybridoma cells were known and readily available to the public at the time of filing. However, since claims 54 and 67 are canceled (without prejudice) by the amendment above, withdrawal of the rejection of claims 54 and 67 under 35 U.S.C. §112, first paragraph, is respectfully requested.

35 U.S.C. §§102(a)

Claims 29 and 38-40 remain rejected, and newly added claims 64 and 72 are newly rejected, under 35 U.S.C. §102(a) as being anticipated by Goel et al. (2000, Cancer Research, 60:6964-6971), which described a tetravalent complex that is formed by non-covalent association of two divalent single chain Fv constructs of antibody CC49 (p. 6965).

The claims are amended to specify an antibody dimer comprising two C_H2 domain-deleted anti-TAG-72 antibodies having the variable region amino acid sequences shown in SEQ ID NO: 7 and SEQ ID NO: 9, which are non-covalently associated to form a tetravalent, dimeric antibody. Goel et al. described divalent, linker-joined scFv constructs of antibody CC49 that associate non-covalently to form a tetravalent complex, but the reference did not describe or suggest an antibody dimer comprising two C_H2 domain-deleted anti-TAG-72 antibodies having a human CH3 domain and the disclosed amino acid sequences as specified in the amended claims.

35 U.S.C. §§102(b)

Claim 29 remains rejected, and newly added claims 64, 65 and 72 are newly rejected, under 35 U.S.C. §102(b) as being anticipated by Mezes et al. (WO 94/13806, 1994), which describes divalent single chain Fv constructs of antibody CC49. Mezes et al. described divalent, linker-joined scFv constructs of antibody CC49 which are assumed by the official action to be

inherently capable of non-covalently associating to form tetravalent dimeric complexes in the manner of the divalent sc(Fv)$_2$ described by Goel et al. However, like the Goel et al. reference, Mezes et al. neither described nor suggested an antibody dimer comprising two C_H2 domain-deleted anti-TAG-72 antibodies having a human CH3 domain and the disclosed amino acid sequences as specified in the amended claims.

Claims 29 and 38-40 remain rejected, and newly added claims 64, 70, and 72 are newly rejected, under 35 U.S.C. §102(b) as being anticipated by Slavin-Chiorini et al. (1993), which described antibody cB72.3ΔCH2, a humanized anti-TAG-72 antibody in which the CH2 domains are deleted and replaced with a spacer of 10 glycine/serine amino acids. The official action considered the ability to non-covalently associate to form a tetravalent antibody complex to be an inherent property of the CH2 domain-deleted antibodies described by Slavin-Chiorini et al. The assumption that anti-TAG-72 antibodies in which the CH2 domains are replaced with a glycine/serine spacer such as those described by Slavin-Chiorini et al. are inherently capable of non-covalently associating to form tetravalent antibody complexes is contradicted by scientific results described in the present application, and in Slavin-Chiorini et al. (1997, Cancer Biotherapy & Radiopharmaceuticals, 12(5):305-316, copy attached). As described in the present application, anti-TAG-72 antibodies in which the CH2 domains are deleted and replaced with a 10-residue glycine/serine spacer do not associate non-covalently to form tetravalent, dimeric antibody complexes (for example, see page 25, lines 23-24). The HPLC sizing data in Figure 9 of the present application shows that chimeric CH2 domain-deleted CC49 antibodies that associate non-covalently to form tetravalent, dimeric antibody complexes elute from a sizing HPLC column in two clearly defined peaks, whereas chimeric CC49 antibodies in which the CH2 domains are replaced with a glycine/serine spacer elute as a single peak, which indicates that they do not associate non-covalently to form dimeric antibody complexes. Slavin-Chiorini et al. (1997) reported that chimeric CC49 antibodies in which the CH2 domains are replaced with a 10-residue glycine/serine spacer also elute from a non-denaturing HPLC sizing column as a single peak (see Figure 3, p. 309), which indicates that the CH2 domain-deleted CC49 antibodies described by Slavin-Chiorini et al. are similarly incapable of associating non-covalently to form tetravalent, dimeric antibody complexes. The assumption of the official action that anti-TAG-72 antibodies in which the CH2 domains are replaced with a glycine/serine spacer are capable of non-covalently associating to form tetravalent antibody complexes is therefore incorrect. Accordingly, the CH2 domain-deleted CC49 antibodies described by Slavin-Chiorini et al. do not anticipate the claimed invention.

35 U.S.C. §103(a)

Goel et al. (2000) alone or further in view of Anderson et al. and Thorpe et al.

Claims 20, 29, 38-40, 51, 53, 54, 59, 63, 64, 66, 67, 72, and 76-79 were rejected under 35 U.S.C. §103(a) as being obvious in view of Goel et al. (2000, Cancer Research, 60:6964-6971), alone or in combination with Anderson et al. (U.S. Patent No. 6,348,581 B1) and Thorpe et al. (U.S. Patent No. 6,342,219 B1).

Goel et al. describes a tetravalent $[sc(Fv)_2]_2$ complex of antibody CC49 formed by non-covalent association two divalent scFv constructs. Anderson et al. describe humanized anti-TAG-72 antibodies and conjugation of such antibodies to cytotoxic agents. Thorpe et al. describe using various types of antibody conjugates for cancer therapy. The kit of claim 20 is allegedly rendered obvious by the disclosure of kit elements by the reference.

As discussed above with respect to the rejection under 35 U.S.C. §102(a), the Goel et al. reference described divalent, linker-joined scFv constructs of antibody CC49 that associate non-covalently to form a tetravalent complex. Goel et al. showed that divalent $sc(Fv)_2$ constructs of CC49 and tetravalent $[sc(Fv)_2]_2$ complexes elute as separate, clearly defined peaks with Mr of 60,000 and 120,000, respectively, upon size exclusion HPLC, whereas CC49 IgG antibodies elute as a single peak with Mr 150,000 (see Fig. 3, page 6966). One of ordinary skill in the art would have recognized that this result indicates that, unlike the divalent $sc(Fv)_2$ constructs described by Goel et al., CC49 IgG antibodies do not associate non-covalently to form tetravalent, dimeric antibody complexes. As described above, Slavin-Chiorini et al. showed that chimeric CH2 domain-deleted CC49 antibodies in which the CH2 domains are replaced with glycine/serine spacers also elute from a non-denaturing sizing HPLC column as a single peak (see Figure 3, p. 309), thereby demonstrating that the CH2 domain-deleted CC49 antibodies described by Slavin-Chiorini et al. also do not associate non-covalently to form tetravalent, dimeric antibody complexes. At the time of filing, a person of ordinary skill in the art would therefore have recognized that divalent $sc(Fv)_2$ constructs are capable of associating non-covalently to form tetravalent dimeric $[sc(Fv)_2]_2$ complexes, but would reasonably have expected that full length IgG antibodies and CH2 domain-deleted antibodies are incapable of associating non-covalently to form tetravalent, dimeric antibody complexes. Therefore, the Goel et al. reference, considered alone or in combination with Anderson et al. and Thorpe et al., would not have described or suggested making or using tetravalent, dimeric, CH2 domain-deleted anti-TAG-72 antibody complexes having a CH3 domain and the disclosed amino acid sequences as specified in the amended claims, to one of ordinary skill in the art at the time the application was filed.

Mezes et al. (1994) alone or further in view of Anderson et al.

Claims 20, 29, 38-40, 51, 52, 59, 63-65, 70, and 72 were rejected under 35 U.S.C. §103(a) as being obvious in view of Mezes et al. (1994), in combination with Anderson et al.

As discussed above, Mezes et al. described divalent scFv constructs of antibody CC49. For the reasons discussed above with respect to the rejection under 35 U.S.C. §103(a) in view of Goel et al. alone or in combination with Anderson et al. and Thorpe et al., the Mezes et al. reference, taken alone or in combination with Anderson et al., also would not have described or suggested making or using tetravalent, dimeric, CH2 domain-deleted anti-TAG-72 antibody complexes having a CH3 domain and the disclosed amino acid sequences as specified in the amended claims, to one of ordinary skill in the art at the time the application was filed.

Slavin-Chiorini et al. (1993) alone or with Anderson et al., Thorpe et al., and Gillies et al.

Claims 20, 29, 38-40, 51, 53-59, 61, 63, 64, 66-72, 74, and 76-79 were rejected under 35 U.S.C. §103(a) as being obvious in view of Slavin-Chiorini et al. (1993), alone or in combination with Anderson et al. (U.S. Patent No. 6,348,581 B1), Thorpe et al. (U.S. Patent No. 6,342,219 B1), and Gillies et al. (1990).

Slavin-Chiorini et al. (1993) described a chimeric anti-TAG-72 antibody (cB72.3ΔCH2) in which the CH2 domain is deleted and replaced with a glycine/serine spacer. The official action stated that the chimeric, CH2 domain-deleted anti-TAG-72 antibodies described by Slavin-Chiorini et al. are considered to be inherently capable of non-covalently associating to form a tetravalent, dimeric antibody complex. The teachings of Anderson et al. and Thorpe et al. are described above. Gillies et al. showed that a CH2 domain-deleted antibody wherein the CH3 domain is fused directly to the hinge region had increased binding activity and shorter half-life.

As discussed above, the assumption that CH2 domain-deleted anti-TAG-72 antibodies such as those described by Slavin-Chiorini et al. (1993) are capable of non-covalently associating to form a tetravalent, dimeric antibody complex is contradicted Slavin-Chiorini et al. (1997), which showed that such CH2 domain-deleted anti-TAG-72 antibodies do not associate non-covalently to form tetravalent, dimeric antibody complexes. This result is corroborated by the present application, which showed that chimeric CC49 antibodies in which the CH2 domain is deleted and replaced with a glycine/serine spacer do not non-covalently associate to form a tetravalent, dimeric antibody complex. Slavin-Chiorini et al. (1993) report that CH2 domain-deleted anti-TAG-72 antibodies comprising a glycine/serine spacer in place of the CH2 domain were relatively stable compared to the CH2 domain-deleted antibodies in which the CH3 domain is directly linked to the hinge region that were described by Gillies et al.

(1990), and suggested that the relative stability of the former CH2 domain-deleted antibodies is due to the present of the peptide spacer (see page 102, left column). One of ordinary skill in the art at the time of filing would therefore have considered that Slavin-Chiorini et al. (1993) taught away from making or using CH2 domain-deleted antibodies lacking a spacer in place of the deleted CH2 domain as described by Gillies et al. The applicants submit that Slavin-Chiorini et al. (1993), alone or in combination with Anderson et al., Thorpe et al., and Gillies et al. (1990), would not have described or suggested making or using tetravalent, dimeric, CH2 domain-deleted anti-TAG-72 antibody complexes having a CH3 domain and the disclosed amino acid sequences as specified in the amended claims, to one of ordinary skill in the art at the time the application was filed.

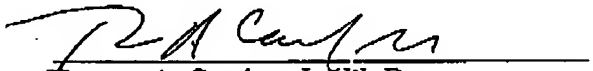
In view of the foregoing, withdrawal of the rejections of the claims under 35 U.S.C. §§102(a), 102(b), and 103(a) stated in the official action is respectfully requested.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,
PILLSBURY WINTHROP SHAW PITTMAN LLP

Date: July 11, 2005



Thomas A. Cawley, Jr., Ph.D.
Registration No. 40,944

P.O. Box 10500
McLean, VA 22102
(703) 905-2144 Direct Dial
(703) 905-2500 Facsimile

TAC/CR